Document made available under the Patent Cooperation Treaty (PCT)

International application number: PCT/IL05/000078

International filing date: 21 January 2005 (21.01.2005)

Document type: Certified copy of priority document

Document details: Country/Office: IL
Number: 160022
Filing date: 22 January 2004 (22.01.2004)

Date of receipt at the International Bureau: 01 March 2005 (01.03.2005)

Remark: Priority document submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b)

World Intellectual Property Organization (WIPO) - Geneva, Switzerland
Organisation Mondiale de la Propriété Intellectuelle (OMPI) - Genève, Suisse

מדינת ישראל
STATE OF ISRAEL

Ministry of Justice
Patent Office

משרד המשפטים
לשכת הפטנטים

This is to certify that annexed hereto is a true copy of the documents as originally deposited with the patent application particulars of which are specified on the first page of the annex.

זאת לתעודה כי רצופים בזה העתקים נכונים של המסמכים שהופקדו לכתחילה עם הבקשה לפטנט לפי הפרטים הרשומים בעמוד הראשון של הנספח.

This 01-02-2005 היום

ממונה על הבוחנים

רשם הפטנטים

Commissioner of Patents

נתאשר
Certified

חוק הפטנטים, תשכ"ז-1967
Patent Law, 5727 - 1967

בקשה לפטנט
Application for Patent

לשימוש הלישכה
For Office Use

מספר: Number	160022
תאריך: Date	22-01-2004
הוקדם/נדחה Ante/Post-Dated	

אני, (שם המבקש, מענו ולגבי גוף מאוגד - מקום התאגדותו)
I, (Name and address of applicant, and in case of body corporate-place of incorporation)

M.D.Z. INVESTMENTS LTD
78 Hadasa St.
Beer-Sheva 84221

מ.ד.צ. השקעות בע"מ
רח' הדסה 78
באר-שבע 84221

Owner, by virtue of **The Law** הדין
of an invention the title of which

שמה הוא

שיטת טיפול בסטומטיטים אפתי בפה ובמוקוסיטים בפה

(בעברית)
(Hebrew)

METHOD FOR TREATING ORAL APHTHOUS STOMATITIS AND ORAL MUCOSITIS

(באנגלית)
(English)

hereby apply for a patent to be granted to me in respect thereof. מבקש בזאת כי ינתן לי עליה פטנט

*בקשת חלוקה - Application of Division	*בקשת פטנט מוסף - Application for Patent Addition	*דרישה דין קדימה Priority Claim		
*מבקשת פטנט from Application	*לבקשה/לפטנט to Patent/Appl.	מספר/סימן Number/Mark	תאריך Date	מדינת האיגוד Convention Country
מס' No. _____	מס' No. _____			
מיום dated _____	מיום dated _____			

*יפוי כח: כללי / ~~מיוחד - רצוף בזה~~ / עוד יוגש
P.O.A.: general / ~~individual - attached~~ / to be filed later

הוגש בעניין filed in case _____

המען למסירת מסמכים בישראל
Address for Service in Israel
לוצאטו את לוצאטו
ת.ד. 5352
באר שבע 84152
מספרנו: 17088/03

חתימת המבקש
Signature of Applicant

היום 21 בחודש ינואר שנה 2004
This of the year

Luzzatto & Luzzatto

By:
Attorneys for Applicant

לשימוש הלישכה

טופס זה כשהוא מוטבע בחותם לישכת הפטנטים ומושלם במספר ובתאריך ההגשה, הינו אישור להגשת הבקשה שפרטיה רשומים לעיל.
This form, impressed with the Seal of the Patent Office and indicating the number and date of filing, certifies the filing of the application the particulars of which are set out above.

*מחק את המיותר Delete whatever is inapplicable

#291679

17088/03

שיטת טיפול בסטומטיטיס אפתי בפה ובמוקוסיטיס בפה

METHOD FOR TREATING ORAL APHTHOUS STOMATITIS AND ORAL MUCOSITIS

METHOD FOR TREATING ORAL APHTHOUS STOMATITIS AND ORAL MUCOSITIS

Field of the Invention

The present invention relates to a composition for ameliorating, treating, and preventing oral mucosa disorders comprising quinoline derivatives.

Background of the Invention

Canker sores, or aphthae, are the most common oral disease which affects, in some degree, up to two thirds of the population, causing discomfort and annoyance to millions of people around the globe. The disease has unclear etiology, and it is also denoted, in various of its symptoms, as recurrent aphthous ulcers (RAU), recurrent aphthous stomatitis (RAS), or ulcerative stomatitis. RAU are characterized by repeated development of painful sores. The small, shallow and rounded ulcers develop inside the mouth, especially on the mucosa of the cheeks, lips, floor of mouth, lateral and ventral sites of the tongue, and only on rare occasions on the gums or the palate. The lesions caused by RAU may reappear at intervals of a few months to a few days. The most common presentation of the disease is minor aphthae (MiRAU) affecting about 80% of RAU patients, which is characterized by recurrent, round, clearly defined, small, painful ulcers, usually less than 5 mm in diameter with a gray-white necrotic

pseudomembrane cover and a thin erythematous halo. MiRAU occur usually on the non-keratinized oral mucosa, i.e., labial and buccal mucosa as well as vestibulum and floor of mouth. These lesions may heal within 10 to 14 days without scarring. Major aphthae (MaRAU) are a less common form of the disease and are usually characterized by recurrent large ulcerations, which may be 1 to 3 cm in diameter. MaRAU occurs mainly on labial, buccal, latero-ventral mucosa of the tongue and may persist up to 6 weeks and often heal with scarring. The third and the least common clinical form of RAU are the herpetiform aphthae (HA) that is characterized by multiple (up to 100) recurrent clusters of pinpoint (2 - 3 mm diameter) painful ulcers, which tend to fuse, producing large areas of erosions and ulcerations. This resembles the clinical presentation of primary herpetic gingivo-stomatitis – a viral disease caused by human herpes virus type I. HA may occur on the entire oral mucosa, including keratinized mucosa, such as that of the gingiva and palate. It has a later age of onset than MiRAU and MaRAU.

From 5% to 66% of the population, depending on the group studied, are afflicted. Studies found that RAU have a tendency to recur along family lines, and a high correlation of RAU has been detected in identical twins [Miller M.F. et al.: Oral Surg. Oral Med. Oral Pathol. 43 (1977) 886-91]. Women seem to be afflicted slightly more then men. The disease seems to be less frequent, e.g., among Bedouin Arabs, but is very common in North

America. Although the etiology of RAU is unknown, numerous systemic and local factors have been proposed to be involved in its pathogenesis. Among the local factors, minor trauma, such as anesthetic injections, sharp foods or trauma from dental treatment, should be considered as one of the precipitating factors of RAU. It has been suggested that oral *Streptococci* and several viruses may play an etiologic role in RAU; however, no conclusive results have been achieved. The involvement of inflammatory cytokines in RAU was implicated [Buno I.J. et al.: Arch. Dermatol. 134 (1998) 827-31]. RAU was also associated with immune disturbances [Eversole L.R. Oral Surg. Oral Med. Oral Pathol. 77 (1994) 555-71]. The systemic and local cellular immunodisregulation associated with RAU seems to be consistent with a viral reactivation, and may be a result of a latent viral infection of oral mucosa [Pedersen A. et al.: Oral Pathol. Med. 22 (1993) 64-8]. RAU was also observed in several systemic disorders, such as Behcet's disease, cyclic neutropenia, MAGIC syndrome, FAPA syndrome, celiac disease, inflammatory bowel disease, HIV, ulcus vulvae acuthum, and hemato-deficiencies, such as iron, zinc, and vitamin deficiencies [Ship J.: Oral Surg. Oral Med. Oral Pathol. Oral Radiol. Endod. 81 (1996) 141-7]. There is no specific treatment for RAU, and the management usually depends on the symptoms, duration and severity of the ulcerative lesions. In cases of RAU resulting from a systemic disorder, the corresponding therapy for said disorder can be efficient, for example in

cases of a nutritional or vitamin deficiency, a replacement therapy is used.

Despite detailed clinical and research investigation over the years, the causes of the disease, first described by Hippocrates, are still unknown, and no effective management is available for it. Therefore, a need is felt for new means that could either heal aphthae or at least ameliorate them more efficiently.

The disorders of mouth mucosa, being manifested by vesicular-bullous ulcerative, or erosive, lesions, may be diagnosed also as chronic discoid lupus erythematosus, herpetiform dermatitis, pemphigus family disorders, pemphigoid family disorders, linear IgA disorders or other immunoregulatory disorders, and similarly to the aphtae family, their etiology is unclear; they are quite common – but less frequent than aphtae. To this greater family of mouth mucosa disorders, radiotherapeutic mucositis and chemotherapeutic mucositis, the conditions caused by radiotherapy and chemotherapy, may be added, even though in this case, etiology is clearer, and involves cytotoxic effects of said therapies. What is common to all the mentioned oral mucosa disorders, including aphthae related disorders, is the lack of knowledge regarding the precise mechanism by which they develop, and the lack of

efficient therapies for these painful conditions. All said mouth mucosa disorders will be called oral mucositis hereinafter.

The most common treatment for oral mucositis of various origin is topical therapy, which may include antimicrobial and analgesic mouthwashes, topical or systemic glucocorticoids, immunosuppressors and hormones. The most common topical therapy is the use of hydrocortisone, triamcinolone, fluocinonide, betamethasone and flumethasone [Scully C. et al.: J. Oral Pathol. Med. 18 (1989) 21-7]. Immunosuppressive drugs, such as colchicine, cyclosporin and thalidomide, as well as immunopotentiating agents, such as levamisole, gammaglobulin and longovital were also tried without clear results. Some topical medications seemed to have certain beneficial effects on the ulcers of RAU, such as sucralfate [Ratan J. et al.: J. Int. Med. 236 (1994) 341-3], azelastine hydrochloride [Ueta E. et al.: J. Oral Pathol. Med. 23 (1994) 123-9], prostaglandin E2 [Taylor L.J. et al.: Br. Dent. J. 175 (1993) 125-9], listerine [Meiller T.F. et al.: Oral Surg. Oral Med. Oral Pathol. 72 (1991) 425-9], diclofenac in hyaluronan [Saxen M.A. et al.: Oral Surg. Oral Med. Oral Pathol. Oral Radiol. Endod. 84 (1997) 356-61], or bioadhesive hydrogel patches [Mahdi A.B. et al.: J. Oral Pathol. Med. 25 (1996) 416-9]. All said treatments are merely palliative, reducing the symptom manifestation. US 5,686,095 discloses a method for topically treating aphthous ulcerations, comprising fluoroquinolone derivatives. Other

topical compositions are known in the art, but so far no efficacious composition has been found.

It is therefore an object of this invention to provide an efficacious pharmaceutical composition for use in ameliorating, treating, and preventing oral aphthous stomatitis and oral mucositis.

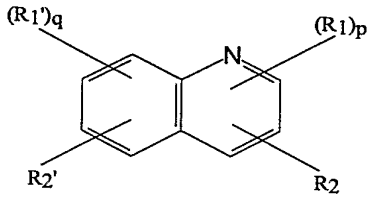
It is further an object of this invention to provide an efficacious pharmaceutical composition for accelerated healing of aphthae, and for mitigating pains caused by them.

Other objects and advantages of present invention will appear as description proceeds.

Summary of the Invention

The present invention provides a pharmaceutical composition for ameliorating, treating, and preventing oral mucosa disorders, including canker sores associated with aphtha minor, aphtha major, recurrent aphthous ulcers (RAU), recurrent aphthous stomatitis (RAS), herpetiform aphthae, vesicular-bullous ulcerative or erosive lesions, pemphigus family disorders, pemphigoid family disorders, linear IgA disorders or other immunoregulatory disorders, herpetiform dermatitis, chronic discoid lupus

erythematosus, radiotherapeutic mucositis, and chemotherapeutic mucositis, comprising a quinoline derivative of formula I:



I

or its stereoisomer, or its pharmaceutically acceptable salt, wherein R_1 and R_1' are independently selected from -H, -Cl, -F, C_1-C_3 alkyl, C_1-C_3 alkyloxy, and $-CF_3$; R_2 and R_2' are independently selected from -H, $-NH(R_3)$, and $-C(OH)(R_3)$, wherein R_3 is selected from phenyl and C_3-C_6 alkyl, substituted with 1 to 3 substituents selected from C_1-C_2 alkyl, ethenyl, -OH, and $-NH_2$, and wherein said $-NH_2$ is either optionally substituted with one or two groups selected from ethyl and hydroxyethyl or the nitrogen atom of said $-NH_2$ is connected with 1 or 2 carbon atoms of said C_3-C_6 alkyl or C_1-C_2 alkyl, possibly forming bicyclic structure; p is an integer from 1 to 3, and q is an integer from 1 to 4.

The composition of this invention may further comprise a component selected from solvents, buffers, carriers, binding agents, stabilizers, adjuvants, diluents, excipients, surfactants, and odorants, as well as a second pharmaceutically active substance selected from analgesic, anti-inflammatory, antiviral, antibacterial, antifungal, antiseptic, and

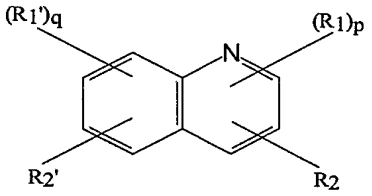
antineoplastic. The composition of this invention is preferably used topically. When it is used systemically, the preferred way is oral delivery.

This invention also relates to a method for treating, ameliorating, and preventing conditions comprising the appearance on the oral mucosa of painful sores, vesicles, bullae, ulcers, erosions, lesions, or blisters, associated for example with aphthae, discoid lupus erythematosus, pemphigus, pemphigoid, herpetiform dermatitis, radiotherapy and chemotherapy, comprising the steps of i) providing a quinoline derivative of formula I as defined above, or its stereoisomer or a pharmaceutically acceptable salt thereof; ii) preparing a formulation comprising said quinoline derivative or its isomer or salt, and further components adjusting the consistency, stability, and olfactory properties, and optionally additional active substances selected from analgesic, anti-inflammatory, antiviral, antibacterial, antifungal, antiseptic, and antineoplastic; and iii) administering said formulation to a patient in need of the treatment. Said administration of said formulation comprises rinsing, spraying, and applying ointment or adhesive patch. A preferred method according to this invention is treating mucosa disorder associated with aphtha, comprising rinsing mouth several times a day with the composition.

Detailed Description of the Invention

It has now been found that some quinoline derivatives are surprisingly effective in treating oral aphthous stomatitis and oral mucositis. In experiments carried out with particular preferred compounds of the invention, the pain caused by ulcerative lesions disappeared often within hours, and the ulcers and other symptoms disappeared usually within days. For example, patients with life-long recurrent aphthae problems achieved quick relief of pains caused by aphthae ulcers after rinsing their mouth with aqueous solutions comprising said compounds.

In a preferred embodiment of this invention, a composition comprising a quinoline derivative of formula I:



I

or a stereoisomer thereof, or a pharmaceutically acceptable salt thereof, wherein

R_1 and R_1' are independently selected from -H, -Cl, -F, C_1-C_3 alkyl, C_1-C_3 alkyloxy, and $-CF_3$; R_2 and R_2' are independently selected from -H, $-NH(R_3)$, and $-C(OH)(R_3)$, wherein R_3 is selected from phenyl and C_3-C_6 alkyl, substituted with 1 to 3 substituents selected from C_1-C_2 alkyl, ethenyl, -OH, and $-NH_2$, and wherein said $-NH_2$ is either optionally

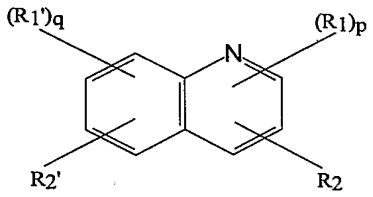
substituted with one or two groups selected from ethyl and hydroxyethyl, or the nitrogen atom of said -NH_2 is connected with 1 or 2 carbon atoms of said C_3-C_6 alkyl or C_1-C_2 alkyl, forming secondary or tertiary amine, possibly forming bicyclic structure; p is an integer from 1 to 3; and q is an integer from 1 to 4;

is applied on oral mucosa afflicted with sores, ulcers, erosions, vesicular-bullous lesions, blisters, stria, or other painful changes, in form of a solution, suspension, gel, emulsion, ointment, patch, or spray. Said solution and suspension are preferably based on aqueous solutions of pharmaceutically acceptable salts and buffers, such as physiological solution, etc, but may contain acceptable non-aqueous solvents, such as ethanol, DMSO, etc. Said gel, emulsion, or ointment may comprise pharmaceutically acceptable oils and surfactants, and are prepared by methods known in the art of topical formulations, therefore not requiring detailed descriptions for their preparations. Said active agent of formula I may be either dissolved in at least one phase of the composition, or may be partially dispersed.

The composition of the invention is applied preferably on the oral mucosa afflicted with a disorder selected from canker sores associated with aphtha minor, aphtha major, recurrent aphthous ulcers (RAU), recurrent aphthous stomatitis (RAS), herpetiform aphthae, vesicular-bullous erosive or ulcerative lesions, pemphigus family disorders, pemphigoid

family disorders (e.g. cicatricial), linear IgA disorders or other immunoregulatory disorders, herpetiform dermatitis, discoid lupus erythematosus, radiotherapeutic mucositis, or chemotherapeutic mucositis. It has been also found that a treatment of mouth mucosa by the quinoline derivatives according to this invention prolongs the symptom-free periods between recurrence attacks.

In a preferred embodiment of the invention, the composition for mitigating and healing symptoms of oral mucositis comprises a quinoline derivative of formula I:

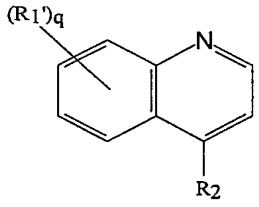


I

wherein R_1 and R_1' are independently selected from -Cl, -OCH_3, and -CF_3; one of R_2 and R_2' is -H and the other is selected from -$NH(R_3)$, and -$C(OH)(R_3)$, wherein R_3 is selected from phenyl and C_3-C_5 alkyl, substituted with 1 to 2 substituents selected from C_1-C_2 alkyl, ethenyl, and -NH_2, and wherein either said -NH_2 is optionally substituted with one or two groups selected from ethyl and hydroxyethyl, or the nitrogen atom of said -NH_2 is connected with 1 or 2 carbon atoms of said C_3-C_5 alkyl or

C_1-C_2 alkyl, possibly forming bicyclic structure; and wherein the sum of p and q is an integer from 1 to 3.

In a preferred embodiment of the invention, the composition for ameliorating or treating or preventing oral mucositis comprises a quinoline derivative of formula II:



II

wherein

R_1' is selected from -Cl, C_1-C_3 alkyloxy, and -CF_3; R_2 is selected from -$NH(R_3)$, and -$C(OH)(R_3)$, wherein R_3 is C_3-C_6 alkyl substituted with 1 to 3 substituents selected from C_1-C_2 alkyl, ethenyl, and -NH_2, and wherein said -NH_2 is either optionally substituted with one or two groups selected from ethyl and hydroxyethyl or the nitrogen atom of said -NH_2 is connected with 1 or 2 carbon atoms of said C_3-C_6 alkyl or C_1-C_2 alkyl, possibly forming bicyclic structure, and wherein q is 1 or 2.

In a preferred embodiment of this invention, oral mucositis is treated by a solution or dispersion comprising hydroxychloroquine (HCQ) or its salt. Preferably HCQ salt is dissolved in an aqueous buffered solution, and used

several times a day for rinsing mouth (without swallowing). The concentration of HCQ or its salt in said solution is preferably from 1 to 10 mg/ml, and the rinsing is preferably performed 3-5 times a day. HCQ is preferably used as sulfate.

In other preferred embodiment of this invention, oral mucositis is treated by a quinine (Q) salt in solution or suspension, which is used several times a day for rinsing mouth (without swallowing). The concentration of Q is preferably from 1 to 10 mg/ml, and the rinsing is preferably performed 3-5 times a day. Said Q solution may comprise Q dihydrochloride, Q hydrochloride, Q sulfate, and other Q salts. Said Q suspension may, for example, comprise Q sulfate. Stereoisomers of quinine and their salts, such as quinidine sulfate, have been also found active.

The invention provides a method for treating a symptom associated with mouth mucositis selected from canker sores associated with aphtha minor, aphtha major, recurrent aphthous ulcers (RAU), recurrent aphthous stomatitis (RAS), herpetiform aphthae, bullous erosive or ulcerative lesions, pemphigus disorders, pemphigoid disorders, linear IGA disorders and other immunoregulatory disorders, chemotherapeutic mucositis, and radiotherapeutic mucositis, comprising preparing a composition containing a quinoline derivative of formula I or a pharmaceutically acceptable salt thereof, in form of paste, cream, gel, patch impregnated

with an active agent, or spray, and applying said composition onto the painful areas or areas afflicted with the pathological changes. Other pharmaceutically effective agents may be present in the composition of the invention, to enhance the healing process, and taking into account eventual other disorders involved. In one preferred embodiment, the method of the invention comprises an adhesive patch impregnated with a composition containing a quinoline derivative of formula I, which patch is placed on the inflicted areas repeatedly, until the pain and other aphthae symptoms disappear. In other very preferred embodiment, mouth rinsing with a liquid composition according to this invention is performed several times a day.

In a preferred use according to this invention, a composition comprising a quinoline derivative, preferably selected from HCQ, quinine, their isomers and derivatives, and their salts, prolong the recurrence periods in persons suffering from RAU. Applying said compositions ameliorates the symptoms, heals ulcers, and typically also prevents the reappearance of new ulcers. For example, in patients suffering up to 10 recurrences per year, the treatment according to this invention led to remission without any exacerbation within four months of follow-up.

A composition according to the invention may comprise a component selected from solvents, buffers, carriers, binding agents, stabilizers,

adjuvants, diluents, excipients, surfactants, flavors, and odorants. In a preferred embodiment of this invention, the composition for treating oral aphthous stomatitis and oral mucositis, comprises another pharmaceutically active substance selected from analgesic, anti-inflammatory, antiviral, antibacterial, antifungal, antiseptic, and antineoplastic compounds; the presence of another active substance may act against some of the causative factors of the disease, or may help in overcoming the secondary problems. In a preferred embodiment said solvents comprise an aqueous solution. Non-aqueous solvents may be used in the composition of the invention, not only to adjust the required consistency of the composition or the solubility of the components, but also to synergistically improve the efficiency of the composition (e.g., DMSO is considered to be anti-inflammatory).

The compositions of this invention may be administered systemically – preferably orally. In a preferred embodiment of this invention, the composition is applied topically, by rinsing the afflicted area or washing the mouth, or alternatively spraying the afflicted area. The time of action of the healing composition of this invention is prolonged when an adhesive patch impregnated with said composition is applied onto the afflicted area.

The invention will be further described and illustrated in the following examples.

Examples

Materials

Hydroxychloroquine (HCQ) was obtained from Sanofi-Syntelabo, Inc. N.Y. USA, quinine (Q) and quinidine sulfate were obtained from Rakah, Holon, Israel. The compounds were used in concentrations 1-10 mg/ml, in tap water.

Example 1

A 40-years-old woman, generally in good health, reported the presence of canker sores for several years (periodic recurrences of 3 to 4 episodes per year). At clinical examination she had a minor aphtha on the vestibular mucosa on the right side of the lower jaw adjacent to teeth #45-46-47. The patient was seen five days after the appearance of the painful aphtha. She started oral rinses with 10 ml of hydroxychloroquine (HCQ) solution, 3.7 mg/ml, three times a day, each rinse for 3 to 5 min. Twenty-four hours after the start of the treatment she was free of any pain, and the aphtha almost disappeared. She continued to rinse for about a week. No additional aphthous lesions appeared during 8 weeks of follow-up.

Example 2

A 30-years-old woman, in otherwise general good health, came with two painful major aphthae, one of 12 mm diameter on the left side of the lower

lip mucosa and the second on the right latero-ventral side of the tongue, about 8 mm diameter. She reported the presence of recurrent aphthous lesions since she was about 8-years-old. During the last year, she continuously suffered from recurrent episodes of major aphthae, with virtually no aphtae-free intervals. Each episode of aphthae usually lasted for 3 to 6 weeks. She started oral rinses with 10 ml of HCQ solution, 3.7 mg/ml, three times a day, each rinse for 3 to 5 min. At clinical examination 5 days later, she reported that the pain completely disappeared 24 hours after the start of rinses. The major aphtha of the lower lip decreased in size to about half its original size and the aphtha of the tongue completely disappeared. At clinical examination after 6 additional days, the major aphtha on the lower lip mucosa disappeared completely, leaving a pronounced scar. Concomitantly, 2 new lesions of minor aphthae, 3 mm in diameter each, were seen, one on the left side of the upper lip mucosa and the other on the ventro-anterior side of the tongue. After 4 more days of rinsing with the same HCQ solution, the aphthous lesion on the tongue disappeared, and that on the lip diminished significantly in its size. These two aphthous lesions did not cause any pain whatsoever. In total, she rinsed with the HCQ solution for 20 days. Follow up for 3 months revealed that no new aphthous lesions were present. The patient reported that this was the longest aphthae-free interval that she remembered during the last years and that her psychological state has significantly improved.

Example 3

A 10-years-old girl, in otherwise general good health, reported the presence of recurrent aphthous lesions of different sizes for the last 2 years. The last episode had been about 3 months before examination. The lesions had disappeared within 2 weeks after using different conventional treatments. At clinical examination, one aphtha of about 3 mm diameter was found on the lower lip mucosa and another one about 6 mm diameter was found on the upper lip mucosa. Both lesions were painful. She started rinsing with 10 ml of HCQ solution, 2.5 mg/ml, three times a day, each rinse for 3 to 5 min. Examination after 5 days revealed that the lesion on upper lip almost disappeared leaving an erythematous area, and the aphtha on the lower lip decreased to about 1 mm diameter. She reported to be free of any pain already after 24 hours from the start of rinsing. She, therefore, was able to eat everything. The patient was advised to continue rinsing with 10 ml of hydroxychloroquine (HCQ) solution, 3.7 mg/ml, three times a day, each rinse for 3 to 5 min for 7 additional days. Within 2 days she reported that the aphtha on the lower lip disappeared completely. She still continued with the rinses for 5 additional days, as recommended. The follow up of 5 weeks after cessation of the rinses did not reveal any new aphthae.

Example 4

A 50-years-old male reported suffering from recurrent episodes of canker sores for many years, with 2 to 3 episodes per year. The last episode had occurred about 6 months before examination. He was diagnosed with diabetes mellitus, so that use of steroidal modalities for treatment of his aphthous lesions was contraindicated. At examination he had a painful major aphthous lesion of about 8 mm diameter at the border of the left lateral side of the tongue and floor of the mouth. He started rinsing with 10 ml of HCQ solution, 1.2 mg/ml, three times a day, each rinse for 3 to 5 min. After 24 hours from start of rinses he was free of any pain and was able to eat everything. After 7 days of rinsing, the aphtha almost disappeared. He remained aphthae-free for 7 months.

Example 5

A 23-years-old man, generally in good health, reports the presence of canker sores since childhood with about 8 to 10 recurrences per year. At clinical examination a minor painful aphtha was present on the mucosa of the lower lip. The ulcer was about 4-5 mm in diameter and was present for 8 days. Common treatment with different ointments did not bring much relief. He started to rinse with 10 ml of hydroxychloroquine (HCQ) solution, 1.2 mg/ml, three times a day, each rinse for 3 to 5 min. After one day of rinses he reported no pain and after three days he reported that the

aphtha completely disappeared. The follow up of 4 months revealed no new aphthae.

Example 6

A 57-years-old male had a minor aphtha on the mucosa of the lingual aspect of tooth #36 close to the floor of the mouth. At clinical examination the lesion was present for about a week. He reported the appearance of such lesions about twice a year. He started to rinse with 10 ml of hydroxychloroquine (HCQ) solution, 2.5 mg/ml, three times a day, each rinse for 3 to 5 min. He reported an almost immediate relief from pain and disappearance of the lesion after 4 days. During 3 months of follow up, no new lesion developed.

Example 7

A 20-years-old woman complained of a very painful canker sore present for two days. At initial clinical examination, a 5 mm in diameter painful ulcer was seen on the right latero-ventral aspect of the tongue. She reported recurrences of such sores once or twice a year. She started to rinse with 10 ml of HCQ solution, 3.7 mg/ml, three times a day, each rinse for 3 to 5 min. The pain disappeared after 24 hours, and the aphtha completely disappeared after 6 days.

Example 8

A 35-years-old woman reported a painful minor aphtha lasting for a week, having appeared 4 months after the previous episode, about 5 mm in diameter in anterior lower right buccal mucosa close to vestibulum. She had tried other medications without improvement. She started oral rinses using 10 ml quinine sulfate, 2.4 mg/ml, three times a day, each rinsing about 3 minutes. She reported the disappearance of pains after two rinses. The clinical examination after 4 days revealed no lesions and complete healing.

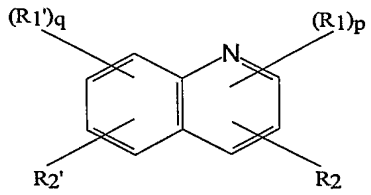
Example 9

A 50-year-old woman had three minor aphthae about 3-4 mm in diameter, all on left buccal mucosa. She was rinsing the site with about 10 ml of quinidine sulfate, 2.4 mg/ml, twice a day. She reported the disappearance of lesions after 4 days.

While this invention has been described in terms of some specific examples, many modifications and variations are possible. It is therefore understood that within the scope of the appended claims, the invention may be realized otherwise than as specifically described.

CLAIMS

1. A composition for ameliorating, treating, and preventing oral aphthous stomatitis and oral mucositis, comprising a quinoline derivative of formula I:



I

or a pharmaceutically acceptable salt thereof, wherein

R_1 and R_1' are independently selected from -H, -Cl, -F, C_1-C_3 alkyl, C_1-C_3 alkyloxy, and $-CF_3$;

R_2 and R_2' are independently selected from -H, $-NH(R_3)$, and $-C(OH)(R_3)$, wherein R_3 is selected from phenyl and C_3-C_6 alkyl, substituted with 1 to 3 substituents selected from C_1-C_2 alkyl, ethenyl, -OH, and $-NH_2$, and wherein said $-NH_2$ is either optionally substituted with one or two groups selected from ethyl and hydroxyethyl, or the nitrogen atom of said $-NH_2$ is connected with 1 or 2 carbon atoms of said C_3-C_6 alkyl or C_1-C_2 alkyl, possibly forming bicyclic structure;

p is an integer from 1 to 3; and q is an integer from 1 to 4.

2. A composition according to claim 1, further comprising a component selected from solvents, buffers, carriers, binding agents, stabilizers, adjuvants, diluents, excipients, surfactants, flavors, and odorants.

3. A composition according to claim 1, further comprising a pharmaceutically active substance selected from analgesic, anti-inflammatory, antiviral, antibacterial, antifungal, antiseptic, and antineoplastic compounds.

4. A composition according to claim 1 for topical use.

5. A composition according to claim 1 for systemic use.

6. A composition according to claim 4, wherein said use comprises cream, ointment, gel, patch, or spray.

7. A composition according to any one of claims 1 to 6, wherein said mucositis comprises canker sores associated with aphtha minor, aphtha major, recurrent aphthous ulcers (RAU), recurrent aphthous stomatitis (RAS), herpetiform aphthae, vesicular-bullous erosive or ulcerative lesions, pemphigus family disorders, pemphigoid family disorders, linear IgA disorders or other immunoregulatory disorders,

herpetiform dermatitis, discoid lupus erythematosus, radiotherapeutic mucositis, or chemotherapeutic mucositis.

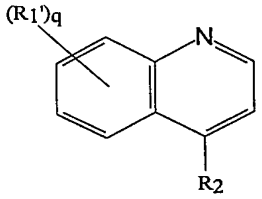
8. A composition according to any one of claims 1 to 7, wherein in said quinoline derivative of formula I, as defined in claim 1,

R_1 and R_1' are independently selected from -Cl, $-OCH_3$, and $-CF_3$;

one of R_2 and R_2' is -H, and one of R_2 and R_2' is selected from $-NH(R_3)$, and $-C(OH)(R_3)$, wherein R_3 is selected from phenyl and C_3-C_5 alkyl, substituted with 1 to 2 substituents selected from C_1-C_2 alkyl, ethenyl, and $-NH_2$, and wherein either said $-NH_2$ is optionally substituted with one or two groups selected from ethyl and hydroxyethyl, or the nitrogen atom of said $-NH_2$ is connected with 1 or 2 carbon atoms of said C_3-C_5 alkyl or C_1-C_2 alkyl, possibly forming bicyclic structure; and

the sum of p and q is an integer from 1 to 3.

9. A composition according to any one of claims 1 to 8, wherein said quinoline derivative has formula II:



II

wherein

R_1' is selected from -Cl, C_1-C_3 alkyloxy, and -CF_3;

R_2 is selected from -$NH(R_3)$, and -$C(OH)(R_3)$, wherein R_3 is C_3-C_6 alkyl substituted with 1 to 3 substituents selected from C_1-C_2 alkyl, ethenyl, and -NH_2, and wherein said -NH_2 is either optionally substituted with one or two groups selected from ethyl and hydroxyethyl or the nitrogen atom of said -NH_2 is connected with 1 or 2 carbon atoms of said C_3-C_6 alkyl or C_1-C_2 alkyl, possibly forming bicyclic structure, and

q is 1 or 2.

10. A composition according to any one of claims 1 to 9, comprising a stereoisomer of a quinoline derivative as defined in claim 1, or a mixture of stereoisomers.

11. A composition according to claim 10, wherein the compound of formula I is selected from quinine, quinidine, hydroxychloroquine, and a salt thereof.

12. A composition according to any one of claims 1 to 11, wherein said mucositis comprises canker sores associated with aphtha minor, aphtha major, recurrent aphthous ulcers, or recurrent aphthous stomatitis.

13. A method for ameliorating, treating, and preventing an oral mucosa disorder, comprising

i) providing a quinoline derivative of formula I as defined in claim 1 or a stereoisomer thereof or a pharmaceutically acceptable salt thereof;

ii) preparing a formulation comprising said derivative of step, components adjusting the consistency, stability, and olfactory properties, and optionally additional active substances selected from analgesic, anti-inflammatory, antiviral, antibacterial, antifungal, antiseptic, and antineoplastic; and

iii) administering said formulation to a patient in need of the treatment.

14. The method of claim 13, wherein said administration of said formulation comprises rinsing, spraying, and applying ointment or adhesive patch.

15. The method of claim 13, wherein said mucosa disorder is associated with aphtha, and wherein said administration comprises rinsing mouth several times a day.

לוצאטו את לוצאטו
LUZZATTO & LUZZATTO